

California M E D I C I N E

OFFICIAL JOURNAL OF THE CALIFORNIA MEDICAL ASSOCIATION

©1954, by the California Medical Association.

Volume 81

DECEMBER 1954

Number 6

Pulmonary Mycotic Infections

Allergic and Immunologic Factors

EDMUND L. KEENEY, M.D., San Diego

• *The mechanisms of immunity and allergy, at play in every infectious disease, must be comprehended before the pathogenesis of an infection can be appreciated.*

Immunity, allergy and serology are concerned with specific antigen-antibody reactions. In immunity the principal concern is with the final disposition of antigen (agglutination, lysis, and phagocytosis). In allergy attention is focused upon tissue damage resulting from antigen-antibody union. In serology interest is devoted to the presence of antibody as evaluated by certain visible *in vitro* reactions—precipitin, agglutination, opsonization and complement fixation tests.

There are two types of allergic reaction—the immediate or anaphylactic type and the delayed type or the allergic disease of infection. Neither kind takes part in the mechanism of immunity. At this time the allergic antibody

and the immune antibody must be considered as two different and distinct antibodies.

Skin and serologic tests are important diagnostic aids in certain pulmonary mycotic infections—for example, coccidioidomycosis, blastomycosis, histoplasmosis and moniliasis.

Clinical expressions of allergy may appear in coccidioidomycosis, histoplasmosis and moniliasis.

Pulmonary mycoses are divided into three groups, that is, the endogenous mycoses (actinomycosis, moniliasis, geotrichosis), the endogenous-exogenous mycoses (cryptococcosis, aspergillosis, mucormycosis) and the exogenous mycoses (nocardiosis, coccidioidomycosis, histoplasmosis, North American blastomycosis).

The diagnosis and treatment of the important mycotic infections that invade lung tissue are discussed.

TO APPRECIATE the pathogenesis of an infectious disease it is essential to have knowledge concerning the mechanisms of natural immunity, acquired immunity and allergy pertinent to the infection under consideration. Such data are not available for all infections but it is helpful to project accessible information for the better understanding of the infectious processes that have not as yet been exhaustively studied. Although these data are available for

certain bacterial and viral infections, there is a paucity of information of this kind with regard to mycotic infections, for they have been less carefully scrutinized than the bacterial and viral diseases.

In any discussion dealing with immunity and allergic sensitivity it is imperative to understand what is meant by the terms *antigen* and *antibody*. Antigens are substances of protein or polysaccharide nature which, upon injection into an animal body, stimulate the formation of antibodies. A molecule to qualify as an antigen must have a molecular

Presented as part of a Panel on Diseases of the Chest before the Section on General Practice at the 83rd Annual Session of the California Medical Association, Los Angeles, May 9-13, 1954.

weight of 10,000 or more, and possess upon its surface a repetition of certain chemical groupings. These chemical groupings determine the specificity of the antigen, and the most important constituent of a group is an acid radical. Any one invading microorganism may be likened to a bag filled with an assortment of different antigens.

An antibody is a plasma globulin molecule. Antibodies, except for their ability to react specifically with antigen, are frequently the same as normal gamma globulin. The concentration and character of antibodies may be assessed by their physicochemical properties; for instance, precipitation by salts, analysis in the ultracentrifuge, and analysis in the Tiselius electrophoresis cell. The presence of antibodies may also be evaluated by a number of serologic reactions. There are five major manifestations of antibody existence to be noted visibly by serologic reactions: (1) antibodies may precipitate soluble antigens (precipitin test); (2) antibodies may cause the aggregation of antigens, if the antigen is in particulate form as part of a bacterial or other cell (the agglutination test); (3) antibody plus the component of normal serum known as complement may cause cells representing antigen to undergo lysis; (4) antibody may bring about a combination of antigen, such as bacteria and other cells, so as to make phagocytosis by leukocytes and macrophages much more effective (the opsonization test); (5) antibody combined with almost any antigen will absorb complement even though the union be an invisible one (the complement fixation test).

There is still a tendency to ascribe the various serologic reactions to the activity of a particular kind of antibody. It is not uncommon to see statements in the literature that "precipitating antibodies," "complement fixating antibodies," and "agglutinating antibodies" are formed during the course of an infection. Such statements simply infer that separate and distinct antibodies are responsible for each of the serologic reactions. This is not always the case. A single antigen in pure state produces only one variety of antibody, and this antibody present in the serum is capable under proper conditions of combining with antigen to produce a variety of serologic reactions. It is not meant to imply, of course, that only one antibody is produced in the body response to invasion by a microorganism; every microorganism is a mixture of many antigens.

The site of antibody globulin formation in the body probably depends upon the nature of the antigen and the route of entrance into the body. At present it is believed that three kinds of cells take part in the manufacture of antibody: reticuloendothelial cells, plasma cells, and lymphocytes.

There are loose concepts in the minds of many that the measure of antibody concentration (titer) by serologic tests measures also the degree of im-

munity. Although the antibodies responsible for eliciting serologic reactions are the same antibodies that neutralize the virulent properties of an offending microorganism, resistance to infection is not always due to antibody. However, serologic reactions do give clues at times to the nature of the potential protective activities of antibodies *in vivo*, and they are of course of great value in providing methods for diagnosing the existence of an infection. The precipitin, the agglutination, and the complement fixation tests are used with advantage in the diagnosis of certain mycotic lung infections. In not a single instance of a fungous infection do these tests measure immunity.

The concepts of the mechanisms of acquired resistance (immunity) are fairly simple ones. The offending organism is possessed of ability to overcome the native resistance of the body, and this act gives the microorganism virulence. The host then acquires antibodies which neutralize the virulence properties; hence the microorganism is finally at the mercy of the body's defenses (phagocytic properties of leukocytes and macrophages). In this scheme we are concerned with a specific antigen-antibody reaction, and our attention is directed particularly toward the final disposition of the antigen.

In all infectious diseases it is not always possible to correlate the presence of antibodies with the immune state. Some other mechanism may function as the harbinger of resistance in place of antibody. For example, humoral factors other than antibodies may be acquired and give resistance, and alterations may take place in the phagocytes which enable them to destroy microorganisms more effectively.

The study of allergy also deals with specific antigen-antibody reactions. In the mechanism of the allergic reaction we are not concerned with what happens to the antigen; we are interested in what happens to the tissue as a result of the antigen-antibody reaction.

As one examines the various manifestations of allergy in man one becomes aware of the different types of reactions and the manner in which these reactions are induced in an allergic person. Some forms of allergic reaction (immediate or anaphylactic type) may be induced by the entrance of a simple antigen into the tissues. Other forms of reaction (delayed type or allergic reaction of infection) are dependent upon the entrance of entire infectious agents into the body.

In the kind of allergy that is established by ordinary and simple antigens, the subsequent response to the same antigen takes place immediately. It is allergy of this type that is present in patients with hay fever, asthma, urticaria, eczema, serum disease, erythema nodosum, erythema multiforme, migrating phlebitis, periarteritis nodosa, rheumatic fever and possibly acute glomerulonephritis. Persons with al-

TABLE 1.—Endogenous pulmonary mycoses.

Disease	Geographical Distribution	Organism	Source	Appearing in Sputum as—	Identified by Cultured Growth on—
Actinomycosis	World wide	<i>Actinomyces Israeli</i>	Tonsils, gums	"Sulphur granules"	Brewer's Thioglycolate medium, 37° C.
Moniliasis	World wide	<i>Candida albicans</i>	Mouth, skin, vagina, gastrointestinal tract	Budding yeast cells, Mycelia	Sabouraud's 30° C.
Geotrichosis	World wide	<i>Geotrichum</i> sp. (species not identified)	Mouth, gastrointestinal tract	Rectangular and spherical cells	Sabouraud's 30° C.

TABLE 2.—Endogenous-exogenous pulmonary mycoses.

Disease	Geographical Distribution	Organism	Source	Appearing in Sputum as—	Identified by Cultured Growth on—
Cryptococcosis	World wide	<i>Cryptococcus neoformans</i>	Soil, skin	Budding yeast cells with wide capsules	Sabouraud's 30° C.
Aspergillosis	World wide	<i>Aspergillus fumigatus</i> (at times, other species)	Soil, grains, grasses, respiratory tract	Broken fragments of mycelium. Small, round conidia	Sabouraud's 30° C.
Mucormycosis	World wide	<i>Mucor corymbifer</i> (at times, other species)	Soil, skin, respiratory tract	Fragments of non-septate mycelium	Sabouraud's 30° C.

lergy of this type have humoral antibodies that may be transferred by means of their serum to normal individuals. Only certain cells of the body become sensitized and take part in the allergic reaction; for example, endothelial cells, smooth muscle cells and collagen. These manifestations are regarded as characteristic of the immediate or the anaphylactic type of allergic reaction.

In the kind of allergic reaction which is dependent upon invasion by the entire infectious agent there are definite characteristics which separate it from the immediate type: The reaction of the tissues to antigen is delayed; humoral antibodies are not present; any cell of the body may be destroyed following contact with antigen. This type of allergic reaction, spoken of as the delayed type or the allergy of infection, is responsible for the tissue damage in tuberculosis, coccidioidomycosis, histoplasmosis, blastomycosis, sporotrichosis, moniliasis and many other infectious diseases. The presence of this kind of allergy is demonstrated by delayed positive reaction to skin test with antigenic materials such as tuberculin, coccidioidin, histoplasmin or blastomycos vaccine.

What then may be the relationship of allergy to immunity? The allergic reaction could be of assistance to the body in resisting an invading micro-organism if the antibody responsible for the allergic reaction were also the antibody responsible for resisting the invasion and progress of the micro-organism. However, this possibility has never been substantiated. It must be concluded at this time that the allergic antibody and the immune antibody are not the same, but are two different antibodies.

The allergic reaction, whether immediate or delayed, might aid resistance to infection if the intense inflammation produced by the allergic reaction could restrict the spread of an infectious agent. Although

it must be generally conceded that inflammation is helpful to the body in impeding the spread of micro-organisms by calling forth rapidly an accumulation of phagocytes, it does not necessarily follow that the exaggerated inflammatory reaction of allergy amplifies protection. It has been ably demonstrated that organisms begin to spread before the allergic reaction takes place and, furthermore, the organisms are spread with the rush of fluids that accompany the violent inflammation. Thus the milder inflammation provoked by the antigenic stimulus in nonallergic tissue is more protective in its localizing attributes than the intense inflammatory reaction of allergy.

There is, therefore, no evidence at this time to consider the allergic reaction as a part of the mechanism of immunity in infectious diseases.

With these fundamental thoughts in mind with regard to allergy, immunity and serologic reactions, one is in a better position to appraise the pathogenesis of infectious diseases. Hence, the signs and symptoms produced by mycotic infections and the diagnostic significance of serologic and skin reactions in these diseases can be more fully appreciated.

The pulmonary mycoses may be divided into three groups, the endogenous mycoses, the endogenous-exogenous mycoses and the exogenous mycoses. Actinomycosis, caused by *Actinomyces Israeli*, moniliasis caused by *Candida albicans*, and geotrichosis caused by species of *Geotrichum* are considered to be endogenous mycoses (Table 1). The fungi responsible for these infections may and do live in various regions of the human body without becoming parasitic. *Actinomyces Israeli* may be found in tonsillar crypts, in dental scum and about carious teeth. *Candida* species are inhabitants of the normal mouth, intestinal tract and vagina, and may be cultured from these sites in 35 to 40 per cent of normal persons. *Geotrichum* species are frequently isolated

TABLE 3.—Exogenous pulmonary mycoses.

Disease	Geographical Distribution	Organism	Source	Appearing in Sputum as—	Identified by Cultured Growth on—
Nocardiosis	World wide	<i>Nocardia asteroides</i>	Soil	Granules. Short and long fragments of mycelium "Spherules"	Veal infusion agar (1% glucose). Sabouraud's 30° C. Sabouraud's 30° C.
Coccidioidomycosis	Southwest U.S.A., Northern Mexico, Argentina	<i>Coccidioides immitis</i>	Soil		
Histoplasmosis	Central U.S.A. In other specific areas of world	<i>Histoplasma capsulatum</i>	Soil	Small yeast-like cells	Sabouraud's 30° C. (cottony). Blood agar 37° C. (yeast-like)
North American Blastomycosis	Southeast U.S.A., Central U.S.A., North America	<i>Blastomyces dermatitidis</i>	Soil	Doubly contoured, granular, budding cells	Sabouraud's 30° C. Blood agar 37° C. (yeast-like)

TABLE 4.—Mycotic infections in which allergy and serology in reactions are important.

Disease	Organism	Clinical Expressions of Allergy	Laboratory Expressions of Allergy Skin Tests with:	Serologic Reactions		
				Precipitin Test Positive	Complement Fixation Test Positive	Agglutination Test Positive
Coccidioidomycosis	<i>Coccidioides immitis</i>	In primary phase: Morbilliform rash, erythema nodosum, erythema multiforme, arthralgia, phlyctenular conjunctivitis	Coccidioidin: Positive	Yes	Yes	Not suitable
Histoplasmosis	<i>Histoplasma capsulatum</i>	In disseminated form: Purpura, urticaria, erythema	Histoplasmin: Positive	Not evaluated	Not evaluated	Not evaluated
North American Blastomycosis	<i>Blastomyces dermatitidis</i>	0	Blastomycin and blastomyces vaccine: Positive	Yes	Yes	Not suitable
Moniliasis	<i>Candida albicans</i>	Asthma, urticaria, eczema	Candidin and Candida vaccine: Positive	Yes	Not evaluated	Yes

from the mouths and the intestinal tracts of patients without disease. The native resistance of the body prevents these microorganisms from becoming invasive. However, native resistance is flexible and in certain circumstances these same fungi may surmount all barriers and proceed to invade, multiply and disseminate through the body. In these respects the endogenous fungi act in a manner similar to staphylococci and streptococci.

There are certain mycotic diseases that may be endogenous as well as exogenous and these are: cryptococcosis, aspergillosis and mucormycosis (Table 2). *Cryptococcus neoformans* has been isolated from apparently normal skin and soil; species of *Aspergillus* are found in the respiratory passages of patients with chronic bronchitis and asthma and in soil and on grains and grasses; species of *Mucor* have been isolated from the respiratory passages and skin of normal persons and in soil.

The endogenous and the endogenous-exogenous fungi, excepting *Actinomyces Israeli* and *Cryptococcus neoformans*, become more virulent when the relationship of the normal flora of the body and their environment is altered by the prolonged administration of the wide spectrum antibiotics.

The exogenous fungi (Table 3) survive and multiply in soil or on plant material. Of the four strictly exogenous mycoses only one, nocardiosis, is rather evenly distributed throughout the world. The remaining fungous infections (coccidioidomycosis,

histoplasmosis, blastomycosis) occur predominately in certain restricted geographical areas. These three mycotic infections have certain common characteristics. For example: They occur mostly in the United States; the gross cultural characteristics of two of the causative organisms (*H. capsulatum*, *B. dermatitidis*) are similar; the allergic reaction of delayed type develops during the course of infection; with moniliasis, they are the only mycotic infections in which a positive reaction to a skin test is a diagnostic attribute; two of the mycoses (coccidioidomycosis, histoplasmosis), with moniliasis, are the only mycoses that have clinical manifestations of the allergic reaction of immediate type during the course of infection; two of the mycoses (coccidioidomycosis, blastomycosis), with moniliasis, are the only mycoses which during the course of infection stimulate the production of the immune type of antibody and they are, therefore, the only mycotic infections in which serologic tests are of diagnostic aid (Table 4). These similarities are recalled not with the purpose of relating the organisms or the infections to one another but expressly to stimulate a scheme of simple thinking about a subject which somehow or other has been made unnecessarily forbidding.

The various mycoses in which pulmonary disease is an important feature will now be discussed individually. No longer do these infections play an unimportant and remote position in medicine and public health. Mycotic infections occur with sufficient

frequency to justify consideration of them in the differential diagnosis of every difficult and complicated pulmonary infection, and even, under certain circumstances, in supposedly benign and simple respiratory diseases.

THE ENDOGENOUS PULMONARY MYCOSES

ACTINOMYCOSIS

The term actinomycosis should refer only to infections that are caused by the anaerobes *Actinomyces Israeli* and *Actinomyces bovis*. Until the appearances of the studies of Erikson,¹¹ of England, and later Thompson,²⁸ of the Mayo Clinic, it was the opinion of the majority of investigators that human and bovine actinomycosis were caused by the same anaerobic microorganism, and depending upon the investigator the organism was referred to either as *Actinomyces bovis* or *Actinomyces Israeli*. However, since the appearance of the sixth edition of "Bergey's Manual of Determinative Bacteriology" in 1948, *Actinomyces Israeli* has been catalogued as the cause of actinomycosis in human beings, and *Actinomyces bovis* as the etiologic microorganism of the bovine infection.

Actinomyces Israeli commonly exists as a saprophyte in the oral cavity and has never been isolated from soil or vegetation. In the mouth the organism is commonly present in and about carious teeth, dental scum, and the crypts of tonsils. From such positions, the organisms may be inhaled or aspirated into the lungs to incite pulmonary infection.

Diagnosis. The primary lesions in pulmonary actinomycosis are usually bilateral and basal, but they may occur unilaterally in any portion of the lung. In the primary site a granulomatous process is induced which usually extends to the mediastinum, pericardium and heart, and/or to the pleura producing pleural pain and occasionally pleural effusion. Eventually the organism invades directly through the pleura to the chest wall, giving rise to numerous draining sinuses. Infrequently the pulmonary infection will be the result of a spread from the primary focus in one or more of the ribs. Rarely in pulmonary actinomycosis is there a spread to the regional lymph nodes, but metastasis by the blood stream to any part of the body may occur.

The diagnosis is established in the laboratory by isolating from the sputum the organism in the form of characteristic "sulphur granules." These granules vary in size and shape and have a radiating lobulated structure and usually, although not always, are yellow in color. They are best observed with a low power microscope lens, but occasionally are large enough to be identified macroscopically or with a hand lens. The interior of the granule does not stand out sharply, but the clubs of the periphery are very refractile and appear as irregular lines marking the

borders of the lobules. By crushing the granule between two slides and then staining with Gram's stain, the Gram-positive branched filaments can be demonstrated. These branched filaments make up the interior of the "sulphur granules."

Actinomyces Israeli is difficult to culture. The sputum should be washed several times with sterile normal saline solution. Suspected granules should be recovered with a bacteriological loop, washed again in sterile normal saline solution, and then placed in Brewer's thioglycollate medium and incubated at 37° C. Colonies that gradually develop appear as fluffy discrete masses of variable size suspended in the media. Mycelia do not project from the surface.

A satisfactory antigenic substance, prepared from the organism or from the broth in which the organism has been grown, has never been isolated. Therefore, skin tests and serological tests, which would be of doubtful diagnostic value anyway for this infection, are not performed.

Treatment. Treatment for the most part is unsatisfactory and consists of indicated surgical drainage, the administration of potassium iodide to the point of intolerance, and x-ray therapy. There are numerous clinical reports in the literature proclaiming the effectiveness of sulfonamides,²² penicillin,¹⁹ aureomycin¹⁷ and chloramphenicol.¹⁶ In the majority of these reported cases surgical measures, iodides, and x-ray therapy supported the sulfonamide and antibiotic therapy, and it is, therefore, impossible to ascribe the entire clinical result to the use of these latter drugs. It must be concluded that necessary surgical intervention, adequate x-ray therapy, and intensive iodide administration are essential adjuncts to antibacterial and antibiotic therapy if optimal results are to be obtained in the treatment of this serious pulmonary infection.

MONILIASIS

Mycologists have replaced the familiar generic term *Monilia* with the name *Candida*. However, the term *moniliasis*, because of its common usage in the medical literature, has been retained in spite of suggestions that *candidosis* or *candidiasis* might be more appropriate. There are seven important species in the genus *Candida* and these are: *albicans*, *tropicalis*, *pseudotropicalis*, *Krusei*, *parakrusei*, *stellatoidea*, and *Guilliermondi*. Only one of these species, *albicans*, is commonly pathogenic for man.

Diagnosis. *Bronchopulmonary moniliasis* is the term employed to designate that type of *Candida* infection of the lungs in which the disease process is limited to the bronchial tree. Infection of this type, which is not at all uncommon, is manifest clinically by the signs and symptoms of ordinary bronchitis. The temperature may be normal or only slightly elevated, and the health of the patient not seriously affected. Pulmonary roentgenograms re-

veal slight to moderate peribronchial thickening. The infection may disappear spontaneously or become chronic and thereby mimic the symptoms of chronic bronchitis of bacterial origin.

Pulmonary moniliasis is the term for infections of the parenchyma of the lungs. While the parenchymal is not so common as the bronchial infection, it is more serious. Pulmonary moniliasis may resemble miliary tuberculosis with cough, fever, dyspnea, pain in the chest, hemoptysis and night sweats. There may be signs of pleural thickening. Areas of consolidation resembling bronchopneumonia may be scattered throughout two or more lobes and, infrequently, there may be lobar consolidation.

The diagnosis of bronchopulmonary and pulmonary moniliasis is fraught with difficulties. Isolation of the organism, particularly if the patient has received antibiotics, is not conclusive. The organism frequently establishes itself in the bronchial mucous membranes as a secondary invader. A diagnosis must be made indirectly by excluding all other conditions, infections and neoplasms that might affect the bronchial and parenchymal tissue, and by repeated demonstration of the organism in the sputum. Actually there are no indisputable criteria for establishing the diagnosis short of the impractical procedure of lung biopsy.

Clinical manifestations of allergic reaction of the immediate type may develop during the course of a *C. albicans* infection. Bronchial asthma was reported by the author¹⁴ to have followed a bronchial infection. The asthmatic symptoms completely disappeared with the alleviation of the infection. The author¹⁵ has also observed the development of urticaria in a patient with cutaneous moniliasis. The author¹⁵ likewise has observed in the past year the development of typical allergic eczema in a two-year-old child one month following the administration of aureomycin. *C. albicans* was isolated from the stools. After the organism was eliminated from the gastrointestinal tract the skin became normal. Eczematoid dermatitis of the face and certain cases of miliaria are thought to be allergic reactions to *Candida* infections. Vesicular lesions on the hands, referred to as moniliids and similar in appearance to dermatophytids, are the result of allergic reactions to infections occurring elsewhere in the body.

Agglutinins and precipitins are occasionally present in the serum of patients with the severe forms of *Candida* infections. However, there are agglutinins for *C. albicans* in the serum of many normal persons. Therefore, serologic tests are of doubtful diagnostic importance. Skin tests are of no value because positive reactions occur in a large proportion of patients without active infection.

The laboratory diagnosis of moniliasis is established by isolating from the sputum budding cells and filaments, and by growing the organism in pure

culture form on Sabouraud's agar. On Sabouraud's medium the organism grows as a yeast, but when stab cultures are made in gelatin or corn meal agar the mycelial form of the fungus is produced. To make certain that the organism isolated is the pathogenic species of *Candida*, it should be tested for fermentation reactions. *C. albicans* will form acid and gas in glucose, acid and gas in maltose, but only acid in sucrose media. Recently a technique was described by Weld²⁹ for the rapid identification of *C. albicans*.

Treatment. Bronchopulmonary moniliasis is best treated with potassium iodide by mouth and sodium caprylate by aerosol. The official solution of potassium iodide should be given in as large a dose as can be tolerated by the patient. One milliliter of a 10 per cent solution of sodium caprylate (New and Non-Official Remedies) should be given by aerosol several times daily. Best results are obtained if a total daily dose of 1 gram is reached.

Pulmonary moniliasis is treated in a manner identical to that of bronchopulmonary moniliasis. Gentian violet should be given intravenously if the patient is not doing well on iodide and caprylate therapy. The dosage is 5 mg. per kilogram of body weight and may be repeated daily or every other day for three to seven doses.

It is usually advisable before administering potassium iodide to give the patient three to four weeks of specific desensitization treatment with *C. albicans* vaccine. The prolonged use of a *C. albicans* vaccine in the management of patients with chronic infections is also advisable.

GEOTRICHOSIS

Geotrichosis is a fungous infection due to one or more species of *Geotrichum*. There has never been a careful study of the saprophytic and pathogenic species of the genus *Geotrichum*. The organism is capable of producing lesions in the mouth, intestinal tract, bronchi and lungs.

Diagnosis. Bronchitis is probably the most frequently recognized manifestation of geotrichosis. The symptoms are identical to those of chronic bronchitis of bacterial origin. The sputum is often gelatinous; the pulse and temperature are rarely elevated; and the general health is good. Medium and coarse rales are noticeable especially at the lung bases. Diffuse peribronchial thickening is a nonspecific condition observed in pulmonary x-ray films.

Invasion of the parenchyma of the lungs brings about signs and symptoms suggestive of pulmonary tuberculosis. The temperature is elevated, the pulse accelerated and the leukocyte content of the blood increased. The sputum is mucopurulent and may or may not contain blood. The physical findings are not specific, but may lead to suspicion of tuberculosis.

Pulmonary roentgenograms reveal patches of infiltration with or without cavity formation.

Microscopic examination of the sputum reveals oblong or rectangular cells with rounded ends and large spherical cells which measure from 4 to 10 microns in diameter. At room temperature on Sabouraud's medium the organism grows rapidly and forms a white to cream colored colony with a dry, mealy surface. Microscopically the hyphae are seen to segment into rectangular arthrospores, which vary in size and roundness of their ends. The rectangular cells ordinarily germinate by a germ tube from one corner. This is a very characteristic finding in cultures of *Geotrichum*.

Treatment. Bronchial infections usually respond rather quickly to iodide by mouth. The official solution of potassium iodide should be administered in the largest dose that can be given with tolerance.

The pulmonary form of the disease should likewise be treated with iodides, but such therapy should not be instituted until tuberculosis has been excluded in the differential diagnosis. If the infection does not respond to iodide therapy an autogenous vaccine should be prepared and immunization carried out. Also in the event that iodides are ineffective, neomycin should be administered. Neomycin has proven effective in the treatment of *Geotrichum* septicemia,¹ and urinary tract infections.¹⁰ It must be emphasized that neomycin is a toxic antibiotic which causes deafness as well as renal damage if administered for more than a short time.

ENDOGENOUS AND EXOGENOUS PULMONARY MYCOSES

CRYPTOCOCCOSIS

The organism responsible for cryptococcosis in man was named *Torula histolytica* by Stoddard and Cutler²⁷ in 1916, and thereafter the disease became known as torulosis. There are now grounds for believing that the organism is not a true *Torula* but instead a *Cryptococcus*. The correct name of the fungus is *Cryptococcus neoformans*, and of the disease it produces, cryptococcosis. However, reports of many cases of this infection will be found indexed under torulosis.

Diagnosis. Clinical manifestations stem from the central nervous system, the respiratory system, the lymphatic system, the skin, the mucous membranes and the bones and joints. Ordinarily a combination of these tissues, rather than just one, is invaded by *C. neoformans*, but the evidence of the involvement of other tissues is usually submerged by the more serious signs of central nervous system disease.

Pulmonary involvement is, in frequency, second only to that of the meninges and brain. It is generally considered that the primary lesion in cryptococcosis occurs in the lungs and that metastasis to

the brain is by way of the blood stream. Cryptococcosis, however, may rarely remain confined to the lung; there are a few reports in the literature attesting this isolation. Of course, it is quite conceivable that pulmonary cryptococcosis might occur without being diagnosed, because few signs or symptoms accompany pulmonary involvement, and the organism is rarely looked for in the sputum unless it has been previously demonstrated in the cerebrospinal fluid. The majority of cases of cryptococcosis of the lungs, therefore, occur in patients who have coexisting lesions in other tissues, especially the central nervous system.

It is common, although not unvarying, for pulmonary cryptococcosis to be accompanied by only meager local and constitutional signs and symptoms. Symptoms when present are those of a cough with some expectoration, and at times with hemoptysis. Occasionally pleural pain may appear or a small effusion be present in the pleural cavity. Rarely does the infection cause disease of clinical severity. Physical signs, if present, are those of bronchitis or of consolidation. Pulmonary roentgenograms are helpful and important in making a diagnosis. In roentgen appearance the lesions may suggest a tumor, a pyogenic abscess or a hydatid cyst. In addition to these shadows there may be linear markings with surrounding woolly shadows, which suggest in turn the findings common in pulmonary moniliasis.

The only exacting proof of pulmonary cryptococcosis is the finding of the organism in the sputum. Fortunately the Ziehl-Neelsen stain is excellent for detecting *C. neoformans* as well as the tubercle bacillus. An India ink preparation of sputum shows up the capsules of the organism brilliantly and thus aids in their identification. Pulmonary cryptococcosis must be differentiated from other chronic lung diseases such as tuberculosis, unresolved pneumonia, pyogenic abscess, bronchitis, bronchiectasis, fibrosis, primary and secondary carcinoma, Boeck's sarcoïd, hydatid cyst and other mycotic infections.

On Sabouraud's media at 30° C. the organism grows slowly. At first the growth is moist, smooth, and cream colored. As the culture ages the color changes to yellow and then to brown. A portion of the culture examined microscopically and in an India ink preparation reveals best the wide typical capsules. This capsule takes on a reddish color when the cells are stained by Gram's technique.

The antibody response in cryptococcosis is poor and consequently precipitin, agglutination and complement fixation tests are of no importance in the diagnosis. With regard to the diagnostic significance of skin tests very little work has been done. The poor antibody response which accompanies this infection is undoubtedly partially responsible for the poor prognosis.

Treatment. There is no specific method of treatment, but this does not imply that a hopeless attitude be assumed. In dealing with a case of cryptococcosis chemotherapeutic tests on mice with all promising drugs should be performed. There is always the possibility that the specific strain of *C. neoformans* isolated will be susceptible to one of the sulfonamides, to one of the antibiotics, to actidione, or to some other drug not yet discovered or synthesized.

Immunization with a vaccine of *C. neoformans* should be tried and continued during the entire course of the disease. If possible a weakly encapsulated strain of the organism should be employed in the vaccine, since there is evidence that vaccines prepared from the weakly encapsulated strains are more immunogenic than vaccines prepared from the strongly encapsulated ones.¹⁸

Pulmonary lesions that are isolated and not part of a generalized infection may heal. However, since the infection is very likely to disseminate, early excision of the circumscribed lesion is advisable.²

Cryptococcus neoformans thrives in an acid medium, and it does not survive temperatures of 105° for seven days or of 107° F. for six days. Accordingly, alkalization and hyperthermia have been suggested as possible methods of treatment. Attempts thus far with alkalization have met with failure and hyperpyrexia has not been adequately tried.

ASPERGILLOSIS

Species of *Aspergillus* are widely distributed in nature and, for the most part, may be considered as saprophytes. Occasionally some species become parasitic and produce inflammatory granulomatous lesions in the skin, the external auditory canal, the paranasal sinuses, the orbit, the bronchi, the lungs and, infrequently, in the bones and meninges.

The disease aspergillosis, which is caused for the most part by *Aspergillus fumigatus*, is world wide in distribution and occurs in persons exposed often to massive doses of the spores; for example, farmers exposed to dust from threshers; fur cleaners employing rye flour as a grease remover; and, in France, the squab feeders who take grain into their mouths to moisten it and, coincidentally, inhale spores.

Diagnosis. Primary pulmonary infection is rare and diagnosis is ordinarily made at autopsy. The clinical symptoms and signs may be those of pulmonary tuberculosis, or other mycotic infections that involve the lungs. There is no clinical characteristic that might lead one to suspect the disease process resulting from invasion by *Aspergilli*.

Direct microscopic examination of sputum reveals broken fragments of hyphae with many small, round, dark green conidia. On Sabouraud's agar at 30° C. the organism grows rapidly, appearing first as a white, cottony growth. As the conidia are produced the color of the colony turns to green or dark

green. Microscopic preparations should be made by placing a small portion of the aerial growth in lactophenol cotton blue and covering with a cover slip. The characteristic swollen conidiophore bearing the sterigmata and then the chains of conidia, which may have been partially broken in making the preparation, can be identified.

Nothing is known concerning the antibody response in humans to infection; consequently, serologic tests remain unevaluated. Positive skin reactions to extracts of *Aspergillus* species, of the immediate whealing type, occur in patients with bronchial asthma, but the significance of reaction of the delayed type and its value in the diagnosis of aspergillosis is unappraised.

Treatment. The official solution of potassium iodide should be given orally in the largest doses that can be tolerated. Prognosis is favorable if the infection is limited to the bronchi, but very poor if there is extensive involvement of the parenchyma of the lung with/or without abscess formation.

MUCORMYCOSIS

The genus of *Mucor*, along with *Rhizopus*, belongs to the family *Mucoraceae*. Molds of this family are frequently referred to as the bread molds and they are found abundantly in soil, manure and on fruits and starchy foodstuffs. Human infections from species of *Mucor* are rare. Of the many species of this genus only a few, notably *M. corymbifer*, are pathogenic.

Diagnosis. In most of the reported cases of human infection due to the *Mucors* only a single organ or system is ordinarily involved. Infection of the lungs is most common, yet there is no clue from the signs or symptoms offered by the infection that might lead one to suspect infection from *Mucor*. As in aspergillosis the findings may suggest pulmonary tuberculosis or other mycotic infections.

The diagnosis of mucormycosis is fraught with difficulties. Even growth of the fungus on culture of the sputum is not unimpeachable evidence of primary infection. The conidia of *Mucor* are airborne and may become laboratory contaminants, and they may reside as saprophytes in the respiratory passages and on the skin. Characteristic fragments of mycelium must be repeatedly demonstrated in sputum or from the region where infection is suspected.

Treatment. A specific form of therapy has never been developed. It is necessary to adapt procedures that have been applied to other mycotic infections.

THE EXOGENOUS PULMONARY MYCOSES

NOCARDIOSIS

The term *nocardiosis* defines infections in man produced by one or several of the species of actinomycetes included in the genus *Nocardia*. The actino-

mycete in this genus which is of interest to the clinician is *Nocardia asteroides*. This organism is common in the soil and it is reasonable to assume that pulmonary infection is initiated by the inhalation of contaminated dust particles. The disease is uncommon but world-wide in distribution.

Diagnosis. In the lung the organism produces bronchopneumonia of a caseating type that may be followed by cavity formation. The clinical picture, therefore, is frequently confused with that of pulmonary tuberculosis. There is a tendency for the organisms to disseminate via the blood stream with the eventual formation of abscesses in many of the organs, particularly the brain. Death is frequently caused by brain abscess. Often the lesions in the lungs are not observed until postmortem examination.

Nocardia asteroides undergoes fragmentation in the sputum and, being acid-fast, the fragments resemble tubercle bacilli. However, the long branched filaments eventually can be found by careful search. The organism grows readily on culture media, but more slowly than bacteria; consequently isolation from sputum by plating is difficult. Pure cultures can be obtained by inoculating guinea pigs with sputum. The animals die after four to nine days and at autopsy miliary white nodules are observed over the omentum and the peritoneal surfaces.

There is no evidence that antibodies are formed as a result of infection. Serologic tests, therefore, are not employed as a diagnostic aid. Asteroidin, which is a broth filtrate of *Nocardia asteroides*, has been employed as a skin testing substance in the experimental infection of guinea pigs and rabbits. Its use as a diagnostic aid in human infections has not been evaluated.

Treatment. The specific measures of treatment are similar to those for actinomycosis produced by *Actinomyces Israeli*. There is one notable exception. Penicillin is not particularly effective in nocardiosis. Sulfadiazine, alone or combined with sulfamerazine, and aureomycin are the drugs of choice.

COCCIDIOIDOMYCOSIS

Coccidioidomycosis is a name originated by Dickson^{8,9} of Stanford University for the disease produced by the fungus *Coccidioides immitis*. The organism produces an acute, usually mild and benign respiratory infection, which is classified as the primary type of coccidioidomycosis. Infrequently, the infection becomes chronic and disseminates to almost any organ, producing therein granulomatous lesions, which progress to such an extent that death occurs in 50 per cent of such cases. This chronic form of the disease is spoken of as progressive or disseminated coccidioidomycosis.

The fungus is present in the dust and soil of the arid and semi-arid regions of southwestern United

States. The light, minute arthrospores which are readily adapted to widespread dissemination, gain entrance into the human body through the respiratory tract, or more infrequently into the skin following trauma. Rodents and other animals in the endemic areas may act as reservoirs for the fungus.

Diagnosis. The symptoms of primary coccidioidomycosis are indistinguishable from those of many acute, mild respiratory infections. Actually the great majority of primary infections are entirely asymptomatic. When symptoms do occur there may be gradations of expression. The incubation period varies from one to three weeks. There is usually fever, which ranges from 99° to 101° F. Pain in the chest is one of the most typical and suggestive symptoms of the disease. Headache, backache, night sweats, anorexia and sore throat are common symptoms. Quite often a morbilliform rash will appear one to two days after the onset of infection. Eight to 14 days following the onset of illness, allergic reactions such as erythema nodosum, erythema multiforme, arthralgia and phlyctenular conjunctivitis may occur. Usually no abnormality is noted upon examination of the lungs. However, in one out of five patients some change in the quality of the breath sounds may be noted. Roentgenograms of the lungs may or may not reveal the following: Thin-walled cavitation usually present in the middle or lower lobes, but rarely above the clavicle; soft infiltrations; enlarged hilar nodes; and fan-shaped densities radiating out from the hilar nodes. If the lung changes present in the primary form persist for six or more weeks, the progressive form of the disease should be suspected. With the progression of the infection the infiltrations increase in size; there is enlargement of the mediastinal nodes; cavities, formerly present, enlarge; cough is pronounced; and the sputum which was scanty becomes more profuse and is occasionally tinged with blood. Approximately 0.1 to 1.0 per cent of the primary cases develop into the progressive form of the disease.

Laboratory studies are helpful in making a diagnosis. There is frequently leukocytosis accompanied by eosinophilia. The sedimentation rate is elevated and ordinarily there is positive reaction to the coccidioidin skin test. Should a positive reaction to skin test occur in a patient with a normal sedimentation rate it is unlikely that the current illness is due to *Coccidioides immitis*. During the recovery phase of the primary infection the lymphocytes rise to 50 per cent or more of the total white blood cell count and the sedimentation rate gradually declines. The precipitin and complement fixation tests are usually positive, but they may be negative in mild infections. Titers of the precipitin and complement fixation tests are high in the progressive form of the disease.

Coccidioides immitis grows on Sabouraud's agar as a white, cottony mold which pigments with age. Old cultures contain myriad large, thick-walled arthrospores (chlamydospores). When these spores are injected into animals they enlarge and become spherical. These large spherical cells, referred to as "spherules," give rise to endospores by cleavage of their cytoplasm. It is the "spherule" that is found in the sputum of the patient infected with *Coccidioides immitis*. It is usually taught that the "spherules" are not contagious. However, investigations recently reported by Rosenthal^{23, 24} indicated that it is well to be suspicious of the old dogma that coccidioidomycosis is never contagious.

Treatment. There is no specific form of therapy for coccidioidomycosis and it can only be hoped that by exercising careful nonspecific measures progression and dissemination of the infection can be prevented. A patient with primary coccidioidomycosis must be kept at absolute bed rest until: (1) the physical symptoms of the infection have disappeared, (2) there is evidence from roentgen examination of the lungs that the lesion has either disappeared or is regressing, (3) the sedimentation rate has returned to normal, (4) the precipitin and complement fixation tests are disappearing or absent.

Most of the patients with the progressive form of the disease die in two to twelve months, but some may recover spontaneously. If patient is extremely sensitive to coccidioidin, that is has a large skin reaction to a 1:1,000 or 1:10,000 dilution, desensitization with this antigen should be given a trial.

HISTOPLASMOSIS

The disease histoplasmosis was first discovered in the Panama Canal Zone by Darling⁵ in 1906. Darling believed the causative organism was a protozoan and gave it the name *Histoplasma capsulatum*. De Monbreun⁶ eventually established that the etiologic organism in histoplasmosis is a fungus. He suggested that a relatively mild and nonfatal form of the disease, similar in nature to the primary and nonfatal form of coccidioidomycosis might exist.⁷ Palmer²⁰ and Christie and Peterson,³ together, were principally responsible for the discovery and recognition of histoplasmosis of the common benign pulmonary type. There are surprisingly few instances of progressive histoplasmosis in view of the many cases of primary pulmonary infection. It is tempting to speculate that the form of the organism that is inhaled is less virulent than the form that enters the body through the skin, mucous membranes, and gastrointestinal tract. The organism has been isolated from the soil and the disease recognized in diversified regions of the United States. It is now the belief that histoplasmosis can exist in any age group, in widespread localities, and can be diag-

nosed where suspicion is alerted and sound mycologic methods are used.

Diagnosis. There are two types of benign pulmonary infection, asymptomatic and symptomatic.

In the *asymptomatic form* the diagnosis is made in retrospect after observing areas of calcification in the pulmonary roentgenograms of patients with positive reaction to histoplasmin skin tests. Although the patients may have positive reaction to tuberculin skin tests it is now generally agreed that pulmonary calcification occurs twice as frequently in association with histoplasmin sensitivity as with tuberculin sensitivity. The pulmonary lesions preceding the areas of calcification are infiltrative and difficult to differentiate from similar lesions occurring in pulmonary tuberculosis. The diagnosis is established by culturing *Histoplasma capsulatum* from the sputum, which is not always easily accomplished. In the event that tubercle bacilli cannot be cultured or demonstrated by direct microscopic technique, histoplasmosis may be suspected. This is especially true if the reaction to a histoplasmin skin test is strongly positive and the tuberculin test is negative or only mildly positive.

In the *symptomatic form* of histoplasmosis the clinical course of the disease and the roentgenologic findings offer a relatively uniform picture. The incubation period is from five to 18 days. The onset of symptoms is rather sudden, with generalized malaise, weakness, vague pain in the chest, nonproductive cough and fever (temperature 102° to 105° F.). There are a few positive physical findings. During the early course of the disease pulmonary roentgenograms reveal the lung fields to be clear, but later disseminated and bilateral lesions varying from fine or mottled granular infiltrations to soft miliary nodules are observed. Cavitation rarely occurs. The lesions tend to calcify in from three to five years after the onset of the acute illness. Even after the acute phase of the illness has disappeared the symptoms of shortness of breath, cough and fatigue often persist for months or even years.

There is some evidence that the symptomatic form may occur in epidemic proportions. Fairly large groups of persons have developed pneumonitis following exposure to the dust of pigeon manure and subsequently *Histoplasma capsulatum* has been isolated from the dust.^{12, 13} Such epidemics simply serve to exemplify that histoplasmosis may occur in epidemic proportions if exposure to dust from soil contaminated with the organism takes place.

The fungus in its parasitic phase is a small yeast-like organism ranging in diameter from 2 to 3 microns. These yeast-like bodies invade the mononuclear cells in enormous numbers. In the sputum the yeast-like bodies are extracellular. Cultures taken from the sputum must be placed on both blood agar

and Sabouraud's media. On Sabouraud's agar at 30° C. the organism produces a white, cottony growth. Spores ranging in size from 10 to 25 microns are produced and from these spores rise finger-like projections 5 microns in length. The growth on blood agar at 37° C. is yeast-like. The gross cultural characteristics of *Histoplasma capsulatum* and *Blastomyces dermatitidis* are similar.

Histoplasmin is a cultural filtrate and contains extracellular antigenic fractions of *Histoplasma capsulatum* produced by growing the organism in a synthetic liquid medium. Skin tests are usually conducted with 1:1,000 and 1:100 dilutions of this broth filtrate. A negative skin reaction to 0.1 ml. of the 1:100 dilution rules out the presence, in the past or at the time of testing, of histoplasmosis. Diagnostic and prognostic attributes of the precipitin and complement fixation tests in human histoplasmosis have not as yet been authenticated.

Treatment. In the pulmonary form of the disease the prognosis is ordinarily good with only non-specific supportive measures of treatment. Only one drug, ethyl vanillate, of the many different therapeutic agents tested, has proven to be effective in the management of the disseminated form of the disease. The original article by Christie⁴ and co-workers should be carefully read before treatment with this drug is given to a patient.

NORTH AMERICAN BLASTOMYCOSIS

North American blastomycosis is a relatively common fungous disease characterized by the formation of granulomatous lesions in the skin, lungs and bones. It is caused by the fungus *Blastomyces dermatitidis*.

Blastomyces dermatitidis is derived from soil and infections develop, for the most part, in persons whose occupations take them into the fields and the forests where contact with the natural source of the saprophytic form of the fungus occurs. Although the greatest incidence of the cases is in the southeastern states and in the Mississippi River Valley area, isolated cases have been reported from nearly every section of the United States as well as from regions in eastern and western Canada.

Diagnosis. The pulmonary form of the disease is often followed by dissemination. The symptoms of pulmonary blastomycosis are insidious and are usually those of an ordinary subacute respiratory infection. There is usually a nonproductive cough, discomfort in the chest, low grade fever and slight dyspnea. With progress of the infection the shortness of breath becomes more annoying, the temperature climbs, and there is loss of weight and strength. Roentgenograms of the lungs frequently disclose enlargement of the mediastinal lymph nodes. Dense masses are frequently observed near the hilum and

project into the lung fields with irregular outlines. The finding of such a hilar mass may quite naturally provoke a diagnosis of bronchogenic carcinoma. As the infection progresses the mediastinum becomes invaded and there is eventually involvement of the pericardium and the heart. The infection may disseminate from the lungs by way of the blood.

The diagnosis is established by demonstrating the organism in the sputum, wherein the fungus occurs only as a round or oval yeast-like cell which reproduces by budding. The cells are easier to demonstrate if the sputum is first treated with 20 per cent sodium hydroxide. The finding of doubly contoured budding cells with granular contents, which in size are slightly smaller than leukocytes, makes the diagnosis certain. Cultures should be made on both Sabouraud's and blood agar media. On Sabouraud's media at 30° C. the colonies first appear smooth and grayish, but they soon become wrinkled, and eventually a white cottony type of growth develops. Cultures on blood agar incubated at 37° C. do not develop filamentous growth but remain yeast-like in appearance.

A blastomyces vaccine or a broth filtrate (blastomycin) prepared in synthetic media from the growing fungus is used for skin testing. Cross reactions between blastomyces vaccine or blastomycin and histoplasmin and coccidioidin are common. This is undoubtedly due to an antigenic fraction common to *Blastomyces dermatitidis*, *Histoplasma capsulatum* and *Coccidioides immitis*. Therefore, regardless of which mycotic infection is suspected, skin tests with blastomyces vaccine or blastomycin, histoplasmin and coccidioidin should always be made. Only those patients very sensitive to coccidioidin (positive reaction to 1:10,000 dilution) give cross reactions with blastomyces vaccine or blastomycin and histoplasmin. Cross reactions between blastomyces vaccine or blastomycin and histoplasmin are very common. However, patients with blastomycosis give larger reactions to blastomyces vaccine or blastomycin than to histoplasmin, and the reverse is true of patients with histoplasmosis.

The complement fixation test is positive during an active infection and the titer rises as the infection progresses. The titer of the test also declines as the patient improves, and disappears with recovery.

Treatment. Pulmonary and systemic blastomycosis are not often favorably improved by x-ray therapy. Patients who are in good general condition with sera containing antibodies that fix complement, usually respond to iodide therapy. Iodides should be given to the point of maximal tolerance and maintained at the largest daily dose that can be administered without symptoms of iodism. Because improvement is very gradual, iodide therapy must be continued over a period of one to three years. Pa-

tients with positive reaction to skin tests with blastomyces vaccine or blastomycin, with or without positive complement fixation tests, usually do not respond to iodide therapy and the disease causes death quickly. However, if these patients are desensitized with blastomyces vaccine and then treated with iodides they ordinarily improve as rapidly as the patients who are not allergic. Patients without positive complement fixation tests and with negative skin tests should receive treatment with blastomyces vaccine until there is a positive complement fixation test. Thereafter, iodide therapy should be given.

Certain diamidines exert an in vitro fungistatic effect on *Blastomyces dermatitidis*,²⁵ and several patients with blastomycosis have been treated with some success with stilbamidine.^{21, 26} This drug, 0.05 gm. to 100 ml. of 5 per cent glucose solution, is given by slow intravenous drip the first day. If this dose is well tolerated, then 0.1 or 0.15 gm. is administered in a similar fashion every day for 10 to 14 days. This course may be repeated if advisable after a two-week period during which the drug is not given. The amount of stilbamidine necessary for cure is not known, but probably a total dosage of 3 to 6 gm. given in two or three courses is enough.

In a high percentage of patients a neuropathic condition involving the trigeminal nerve appears two to five months after treatment with stilbamidine. The sensation to touch is lost but sensations to pain, temperature and pressure remain intact. The sensory changes may persist indefinitely.

Although stilbamidine is the first drug of choice in the treatment today of all cases of pulmonary blastomycosis, regardless of the immunologic and allergic status of the patient, physicians must be ever mindful that its use represents a new form of treatment and, therefore, its dangers and limitations have not at this time been entirely evaluated.

1540 Sixth Avenue, San Diego 1.

1. Bendove, R. A., and Ashe, B. I.: *Geotrichum septicemia*, Arch. Int. Med., 89:107, 1952.

2. Berk, M., and Gerstl, B.: *Torulosis (cryptococcosis) producing a solitary pulmonary lesion: report of a four-year cure with lobectomy*, J.A.M.A., 149:1310, 1952.

3. Christie, A., and Peterson, J. C.: *Pulmonary calcification in negative reactors to tuberculin*, Am. J. Pub. Health, 35:1131, 1945.

4. Christie, A., Middleton, J. G., Peterson, J. C., and McVickar, D. L.: *Treatment of disseminated histoplasmosis with ethyl vanillate*, Pediatrics, 7:7, 1951.

5. Darling, S. T.: *A protozoan general infection producing pseudotubercles in the lungs and focal necrosis in the liver, spleen and lymph nodes*, J.A.M.A., 46:1283, 1906.

6. De Monbreun, W. A.: *The cultivation and cultural characteristics of Darling's Histoplasma capsulatum*, Am. J. Trop. Med., 14:93, 1934.

7. De Monbreun, W. A.: *The dog as a natural host for Histoplasma capsulatum*, Am. J. Trop. Med., 19:565, 1939.

8. Dickinson, E. C.: *Coccidioides infection*, Arch. Int. Med., 59:1029, 1937.

9. Dickson, E. C., and Gifford, M. A.: *Coccidioides infection (coccidioidomycosis)*, Arch. Int. Med., 62:853, 1938.

10. Duncan, G. G., Clancy, C. F., Wolgamot, J. R., and Beidleman, B.: *Neomycin: results of clinical use in ten cases*, J.A.M.A., 145:75, 1951.

11. Erikson, D.: *Pathogenic anaerobic organisms of the Actinomyces group*, Med. Research Council, Special Report Series No. 240, London, His Majesty's Stationery Office, 1940.

12. Feldman, H. A., and Sabin, A. B.: *Pneumonitis of unknown etiology in group of men exposed to pigeon excreta*, J. Clin. Invest., 27:533, 1948.

13. Furcolow, M. L., and Larsh, H. W.: *Direct isolation of Histoplasma capsulatum from soil: probable etiological relationship to Camp Gruber pneumonitis*, Proc. Soc. Exp. Biol. and Med., 80:246, 1952.

14. Keeney, E. L.: *Candida asthma*, Ann. Int. Med., 34:223, 1951.

15. Keeney, E. L.: *Practical Medical Mycology*. Charles C. Thomas, Springfield, Ill. To be published.

16. Littman, M. L., Paul, J. S., and Fusillo, M. H.: *Treatment of pulmonary actinomycosis with chloramphenicol (chloromycetin): report of a case*, J.A.M.A., 148:608, 1952.

17. McVay, L. V., Jr., and Sprunt, D. H.: *A long-term evaluation of aureomycin in the treatment of actinomycosis*, Ann. Int. Med., 38:955, 1953.

18. Neill, J. M., Abrahams, I., and Kapros, C. E.: *A comparison of the immunogenicity of weakly encapsulated and of strongly encapsulated strains of Cryptococcus neoformans (Torula histolytica)*, J. Bact., 59:263, 1950.

19. Nichols, D. R., and Herrell, W. E.: *Penicillin in the treatment of actinomycosis*, J. Lab. and Clin. Med., 33:521, 1948.

20. Palmer, C. E.: *Nontuberculous pulmonary calcification and sensitivity to histoplasmin*, Pub. Health Rep., 60:513, 1945.

21. Pariser, H., Levy, E. D., and Rawson, A. J.: *Treatment of blastomycosis with stilbamidine*, J.A.M.A., 152:129, 1953.

22. Poulton, E. P.: *Discussion of treatment of bacterial diseases with substances related to sulphanilamide*, Proc. Roy. Soc. Med., 31:149, 1937.

23. Rosenthal, S. R., and Routien, J. B.: *Contagiousness of coccidioidomycosis: an experimental study*, Arch. Int. Med., 80:343, 1947.

24. Rosenthal, S. R., and Elmore, F. H.: *Studies on the contagiousness of coccidioidomycosis. II. The fate of spherules in sputum, exposed out of doors. III. Infection in guinea pigs by contact with diseased animals*, Am. Rev. Tuberc., 61:95, 1950.

25. Schoenbach, E. B., and Greenspan, E. M.: *Pharmacology, mode of action and therapeutic potentialities of stilbamidine, pentamidine, propamidine and other aromatic diamidines*, Medicine, 27:327, 1948.

26. Schoenbach, E. B., Miller, J. M., and Long, P. H.: *Treatment of systemic blastomycosis with stilbamidine*, Ann. Int. Med., 37:31, 1952.

27. Stoddard, J. L., and Cutler, E. C.: *Torula infection in man. Studies from the Rockefeller Institute for Med. Research*, Reprints, 1:25, 1916.

28. Thompson, L.: *Isolation and comparison of Actinomyces from human and bovine infections*, Proc. Staff Meet. Mayo Clin., 25:81, 1950.

29. Weld, J. T.: *Candida albicans. Rapid identification in pure cultures with carbon-dioxide on modified eosin-methylene blue medium*, Arch. Dermat. and Syph., 66:691, 1952.